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NEURONAL PLASTICITY

Upscale, downscale

> with time, the profile of changes in protein expression in response to a treatment becomes more distinct

The strength of neuronal synapses scales up or down in response to global decreases or increases in presynaptic activity, respectively. However, the mechanisms involved in this homeostatic synaptic scaling are incompletely understood. Now, Schuman and colleagues characterize changes in protein expression in neurons exhibiting synaptic upscaling or downscaling.

The authors used BONCAT (bio-orthogonal non-canonical amino acid targeting) to metabolically label and identify nascent proteins in cultured rat neurons that were either untreated or incubated for 2 hours with the sodium channel blocker tetradotoxin (TTX) or the $GABA_A$ receptor antagonist bicuculline. Whereas TTX decreases neuronal activity and therefore promotes synaptic upscaling, bicuculline increases overall neuronal activity and thus drives synaptic downscaling. Through the use of this approach, the authors found that these treatments altered the levels of 168 proteins. Whereas some proteins were regulated in the same direction by both treatments, others were regulated uniquely by one of the treatments, or were differentially regulated by the different treatments.

Next, the authors used gene ontology terms to identify functional protein classes that showed differences in expression with scaling. Of the 168 treatment-regulated proteins, 152 were associated with neuronal functions, and the top 20 functional classes featured several clusters involved in the secretory pathway and synaptic function. TTX upregulated and bicuculline downregulated the expression of voltage-gated calcium channels and synaptosome- and dendritic spine-related proteins, whereas bicuculline upregulated and TTX downregulated many proteins involved in translation.

To investigate how scaling-related proteomic changes might change over time, the authors compared their data with previously obtained proteomic data from neurons incubated with TTX or bicuculline for 24 hours. A total of 307 proteins were regulated by the treatments at 24 hours. Compared with the 2 hour time point, different groups of proteins were upregulated or downregulated at 24 hours, with only 10 proteins displaying significant differential regulation at both time points. However, the different sets of proteins regulated at the 2 hour or 24 hour time points belonged to the same functional groups. Thus, with time, the profile of changes in protein expression in response to a treatment becomes more distinct, and neurons use different proteins of the same functional groups for upscaling or downscaling.

The authors computationally clustered the patterns of treatment-induced changes in expression of each of the regulated proteins at each time point; this generated 12 distinct protein response profiles. Of these, 11 carried information about the duration of the treatment and 7 indicated the polarity of the scaling response, with 6 profiles indicating treatment duration and scaling polarity.

Last, the authors examined interactions among the regulated proteins and identified several scaling-regulated functional networks, including those related to intercellular communication, mitochondrial translation and neuronal systems. Moreover, several of the regulated proteins have many protein interactors and thus, the authors note, could have multiplicative effects during synaptic scaling.

Together, these findings create a detailed picture of the proteomic changes associated with homeostatic scaling of synapses in response to increases or decreases in activity.

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ORIGINAL ARTICLE Schanzenbächer, C. T., Langer, J. D. & Schuman, E. M. Time- and polarity-dependent proteomic changes associated with homeostatic scaling at central synapses. *eLife* **7**, e33322 (2018)

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